21 26
~~23~~. The protein of claim ~~22~~ wherein said β and α subunits are linked in head-to-tail configuration.

22 21
~~24~~. The protein of claim ~~23~~ wherein one of m and n is 0 and the other is 1 and wherein the linker is CTP.

23
~~25~~. The protein of claim 1 which is of the formula α-(linker^1)$_m$- β^1-(linker^2)$_n$-β^2 (3).

24 23
~~26~~. The protein of claim ~~25~~ wherein said β and α subunits are linked in head-to-tail configuration.

25 24
~~27~~. The protein of claim ~~26~~ wherein one of m and n is 0 and the other is 1 and wherein the linker is CTP.--

REMARKS

The claims have been amended in response to some of the rejections under 35 USC 112, second paragraph, and further to clarify the invention. The claims have been renumbered in this response as the Office action indicates that claims 7-17 had been renumbered as 6-16. Applicants appreciate the Examiner's noticing and correcting the numbering error.

Applicants appreciate the recognition that the claimed subject matter is free of the art. The invention lies in providing single-chain forms of the glycoprotein hormones TSH, FSH, LH and CG with two β subunits included. Such constructions permit, but do not require, bifunctionality of the resulting single-chain proteins.

The Rejections under 35 USC 112, Second Paragraph

Claim 1 was objected to as indefinite on the basis that the receptor to which agonist or antagonist activity was exhibited was not clearly specified. This has been clarified in claim 1; since claims 11, 16 and 17 (or 11, 15 and 16, as renumbered) are dependent ultimately on claim 1, this explicit limitation is incorporated into these claims as well.

Claim 3 has been canceled.

With respect to claim 4's recitation of a position "proximal" to its C-terminus, it is believed unnecessary to insert the specific definition set forth in the specification into the claim. Page 9, line 26 explicitly sets forth an upper limit to "proximal." Thus, by definition, the word means within 10 amino acids of that terminus. The preferred embodiments, which are not claim limitations, are within 5 amino acids or at the terminus *per se*.

With respect to the asserted ambiguity in the definition of "partial CTP unit," reconsideration is requested. This ambiguity does not, in fact, exist; a "partial" CTP unit is not a "variant." It has its own definition which is specifically that set forth on page 10, lines 6-15. There is no limitation in this definition that only 10 amino acids can be deleted.

The asserted lack of clarity in claim 5 has been obviated by amendment.

Original claim 7 (now claim 6) has been clarified by amendment.

Former claim 8 (now claim 7) has been amended as kindly suggested by the Examiner.

The foregoing amendments and discussion are believed to obviate the rejections under 35 USC 112, second paragraph.

The Rejections under 35 USC 112, First Paragraph

Applicants appreciate the recognition that the pending claims are enabled for single-chain proteins of the formula β^1-(linker^1)$_m$-α-(linker^2)$_n$-β^2 wherein α, β^1, and β^2 represent α and β units of LH, FSH, TSH and CG. Applicants take this recognition at face value and thus assumes that claims of the scope of proposed new claim 17 and claims dependent thereon are free of this rejection.

It is believed the rejection as applied to the remaining formulae is addressed by the enclosed Declaration under 37 CFR §1.132. This Declaration describes the results of experiments testing the ability of two different proteins which fall under generic formula (2) to bind to the appropriate receptors. In both cases, the receptor for each of the β subunits contained in the construct is successfully bound.

It appears that the Office does not question the teaching and written description of the compounds of formulas (2) and (3) in addition to those of formula (1). Attention is called to page 12, beginning at line 19, which sets forth examples of alternative embodiments of formulas (2) and (3). Thus, the construction of such embodiments is clearly taught. What the Office

appears to be questioning is whether or not there is proof that such embodiments will be effective as agonists or antagonists. The application does teach that these embodiments do have these activities. The Declaration submitted herewith confirms this.

Turning, however, to the specific criticisms set forth in the basis for rejection, applicants respond as follows.

(a) The claims have been amended to recite specifically the 4 glycoprotein hormones intended all along. It is believed that the specification makes clear, beginning at page 4, line 23, that this is the intent.

(b) Applicants do not understand why there is an issue with respect to nonrecombinantly produced proteins. It is understood from the interview that this basis for rejection will be reconsidered. Certainly it is well known that proteins of any arbitrary length can be synthesized using commercially available solid-phase technology, as well as using a number of well known solution-phase systems. There is no necessity for using DNA technology to construct the proteins of the invention, although in many cases this is the most convenient approach. It is specifically noted on page 17, lines 14-24, that nonrecombinant methods can be used to synthesize these proteins, although this would be readily apparent to the skilled artisan. Clearly, however, the recombinant approach cannot be used if nongene-encoded amino acids are included in the proteins or if the linkers are not themselves amino acid sequences or if the subunits are linked in head-to-head or tail-to-tail configuration. This is set forth in some detail beginning at page 5, line 20-page 6, line 5. This paragraph merely alludes to what the skilled artisan would certainly know, that methods to synthesize nonfusion proteins of this type are well within ordinary skill. See also page 17, lines 14-24 cited above. Surely the Office does not question that such embodiments could be made. The text of the rejection, however, implies that the basis is other than failure to teach how to make, but rather how to select the appropriate components, in particular, the linker. This is discussed further in response to paragraph (d).

(c) The Office then questions the question of the arrangement of the subunits on the basis that the working example is of the sequence β-α-β and has been demonstrated to be operable. Applicants understand from the interview that this issue is resolved by the enclosed Declaration.

(d) Applicants agree with the point of view expressed by the Examiner that the nature of the linker is relevant to the operability of the claimed proteins. Applicants do not agree, however, that the selection of suitable linkers would require undue experimentation. As indicated in the working example, operable embodiments may not involve any linkers at all. It is well within ordinary skill to select a linker of appropriate functionality and hydrophilicity/ hydrophobicity. This is discussed on page 12, lines 4-16. It is believed that this paragraph provides adequate guidance. The characteristics required by the linker are set forth in that paragraph.

Applicants can only agree enthusiastically that the ordinary artisan would be able to suggest possible linkers which would be expected to be neutral in effect. It is therefore understood by applicants that this aspect of the rejection is withdrawn. Claim 3, drawn specifically to linkers which include drugs, has been canceled to expedite prosecution.

(e) With respect to truncated forms, it will be noted that former claim 7 (now claim 6) has been amended to specify deletions of only 1-10 amino acids at the N or C terminus, and to require retention of binding function. Thus, any issue relates only to variants. While the Examiner may be correct that the number of possible nonfunctional variants of each individual subunit would vastly outnumber functional variants (although this is not, in fact, true), this is not the issue. As the Examiner recognized, the specification sets forth a review of the knowledge in the art, which is extensive, as to what does and does not make a successful variant. Thus, the ordinary practitioner would not find it necessary to explore the success or failure with respect to all *possible* variants; sufficient guidance is provided by the art to focus the attention of the artisan on variants that would, indeed, be operable. The criticism that what could be considered "noncritical" regions may actually be needed to obtain the proper three-dimensional configuration of the protein is believed in error. To the extent that the configuration of the protein is important in its heterodimeric state, as well as in the single chain form, these regions would not be identified as "noncritical".

(f) Applicants appreciate the acknowledgment that the specification is enabling of pharmaceutical compositions comprising proteins which act as agonists or antagonists of LH, CG, TSH or FSH. It is understood that the cancellation of claim 3 obviates this aspect of the rejection.

In view of the foregoing, it is believed that the rejection under 35 USC 112 may properly be withdrawn.

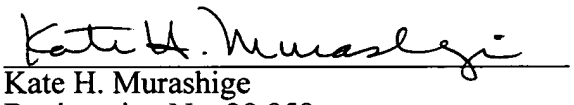
Conclusion

The claims have been amended in response to criticisms of lack of clarity. Further, it is believed that the invention as claimed, for the reasons stated above, is claimed in a manner consistent with 35 USC 112, first paragraph. There is no art rejection. Thus, it is respectfully submitted that claims 1-8 and 10-27 are in a position for allowance and passage of these claims to issue is respectfully requested.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, applicants petition for any required relief including extensions of time and authorizes the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket no. 295002005600. However, the Assistant Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Respectfully submitted,

Dated: March 2, 1999

By: 

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